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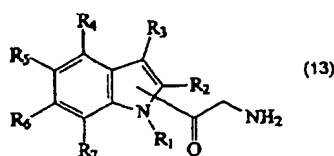
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(54) Title: **METHODS FOR MAKING BIS-HETEROCYCLIC ALKALOIDS**



**WO 01/94310 A1**

(57) Abstract: Methods for making bis-heterocyclic compounds, especially bis-heterocyclic compounds having five and six-membered heterocyclic linkers are described (formula (13)). Also described are methods for making an alpha amino ketone synthon that enables facile syntheses of bisindole compounds, including topocentins and dragnacidins.

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## METHODS FOR MAKING BIS-HETEROCYCLIC ALKALOIDS

### FIELD

The present invention concerns bis-heterocyclic alkaloids, including  
5 bisindole compounds, and methods for their synthesis.

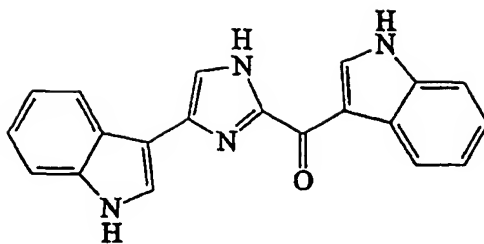
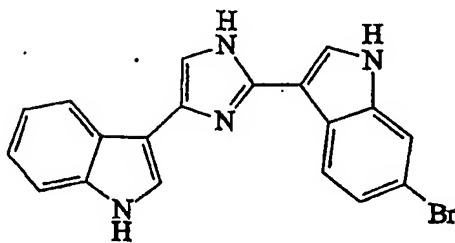
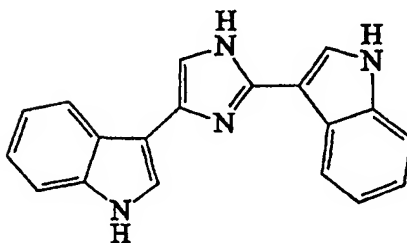
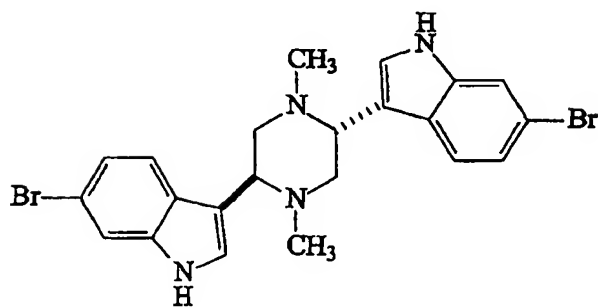
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funds provided by the National Institutes of Health under contract number GM  
10 50929. The United States government may have certain rights to this invention.

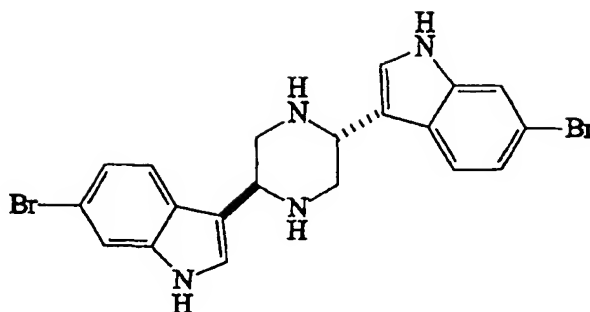
### BACKGROUND

Marine sponges produce a number of bioactive, bisindole metabolites  
containing either an imidazole- or a piperazine- derived linker unit. These  
15 compounds have received much attention due to their potent biological activities as  
antitumor, antiviral, and antiinflammatory agents. The bisindole alkaloid topsentin  
A 1 is representative of a class of deep-sea sponge bisindole metabolites that contain  
an imidazole linker. The nortopsentins, including nortopsentin B 2 and nortopsentin  
D 3, also are examples of bisindole sponge metabolites with an imidazole linker.  
20 The 2,5-bis(3'-indolyl)piperazine alkaloids, dragmacidin B 4 (from the sponge,  
*Hexadella* sp.) and 2,5-bis(6'-bromo-3'-indolyl)piperazine 5 (from the tunicate,  
*Didemnum candidum*) are representative of a group of bisindole metabolites  
containing a piperazine linker. Biosynthetically, dragmacidins and topsentins are  
conceivably derived by the condensation of two tryptamine derivatives in either a  
25 head-to-head (topsentins) or head-to-tail (dragmacidins) orientation.

- 2 -

**Compound 1****Compound 2****Compound 3****Compound 4**

- 3 -



Compound 5

Previous syntheses of bis(indolyl)imidazoles have been accomplished via  
5 palladium-catalyzed cross coupling of 3-indolylboronic acids or 3-stannylindoles  
with halogenoimidazoles (See, for example, Kawasaki et al., *J. Chem. Soc., Chem.  
Commun.*, 1994, 2085), rearrangement and dimerization of hydrazinium bromide  
prepared from 3-bromoacetylindole (See, for example, Braekman et al., *Pure &  
Appl. Chem.*, 1989, 61, 509), and oxidative dimerization of 3-hydroxyacetylindoles  
10 using  $\text{Cu}(\text{OAc})_2$  and  $\text{NH}_4\text{OH}$  (See, for example, Tsugi, et al., *J. Org. Chem.*, 1998,  
53, 5446).

Despite the broad range of biological activity exhibited by the class of  
bis(indolyl)piperazines, including cytotoxicity, only two reports have described the  
successful construction of the piperazine ring system (See, Witlock and Cava  
15 *Tetrahedron Lett.*, 1994, 35, 371 and Jiang et al, *J. Org. Chem.*, 1994, 59, 6823). In  
both reports, access to the substituted piperazines was achieved via diborane  
reduction of diketopiperazine intermediates.

### SUMMARY

20 The present invention provides methods for making compounds that have a  
structure according to the general formula:



- 4 -

wherein A<sub>1</sub> and A<sub>2</sub> are heterocycles and M is a linker moiety that joins the two heterocycles, A<sub>1</sub> and A<sub>2</sub>, into a bis-heterocyclic compound. The heterocycles, A<sub>1</sub> and A<sub>2</sub>, can be the same or different. The heterocycles A<sub>1</sub> and A<sub>2</sub> can be, for example and without limitation, indole, pyridine, pyrimidine, purine, pyrrole, furan, thiophene, imidazole, benzimidazole, oxazole, thiazole, pyrazole, 3-pyrroline, pyrrolidine, quinolone, isoquinolone, carbazole, cyclic anhydride, cyclic imide, cyclic lactone, and the like. The heterocycles can be aromatic or non-aromatic. If the heterocycles A<sub>1</sub> and A<sub>2</sub> comprise indole, the compound is a bisindole compound. The heterocycles can be joined to the linker moiety at any position on the heterocyclic ring. When the linker moiety comprises a ring structure, the heterocycles A<sub>1</sub> and A<sub>2</sub> can be joined thereto at any position on the linker moiety.

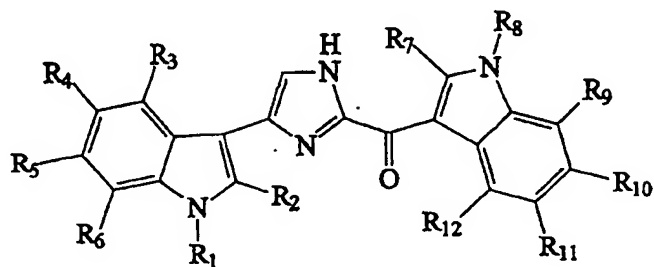
In particular embodiments, methods are provided for making bisindole compounds of the general formula:

Indole - M - Indole

wherein linker moiety M, for disclosed embodiments, typically comprises a ring structure selected from the group consisting of pyrazine, piperazine, imidazole, and oxazole. The indole rings may be joined to the linker moiety at any position on the indole rings and any position on the ring of the linker moiety. In other particular embodiments the linker moiety comprises an amide and the indole rings may be joined to the linker moiety at any position on the indole rings.

- 5 -

In some embodiments, methods are provided for making bisindole compounds of Formula 1.

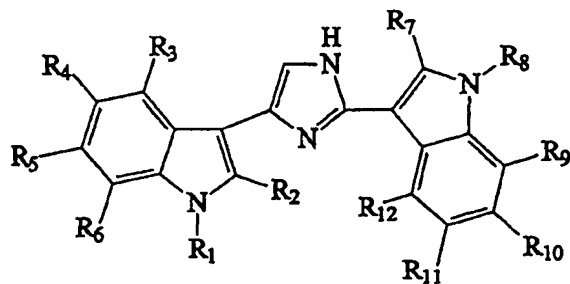


Formula 1

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Compounds with Formula 1 are referred to herein as topsentins.

In other embodiments, methods for making compounds of Formula 2 are disclosed.



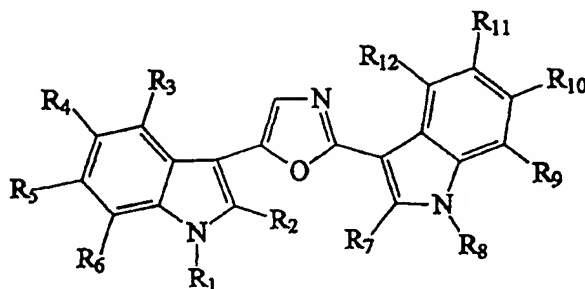
Formula 2

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Compounds with Formula 2 are referred to herein as nortopsentins.

- 6 -

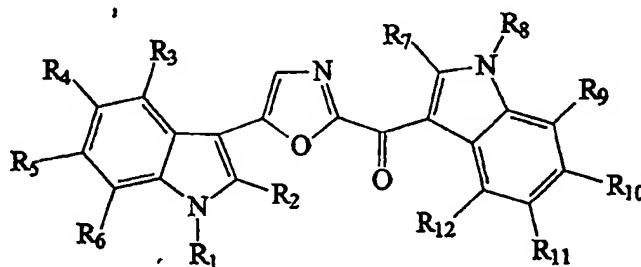
In some embodiments, methods for making bisindole compounds of Formula 3 are disclosed.



Formula 3

5

In other embodiments, methods for making bisindole compounds of Formula 4 are disclosed.



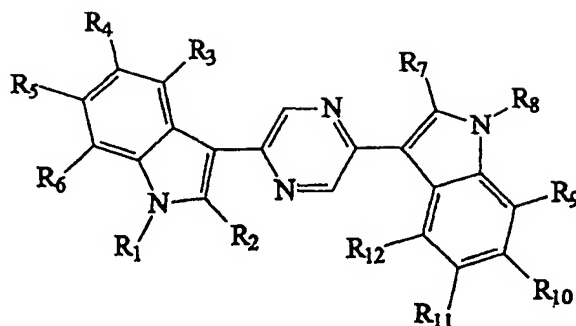
Formula 4

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In some embodiments, methods for making bisindole compounds of Formula

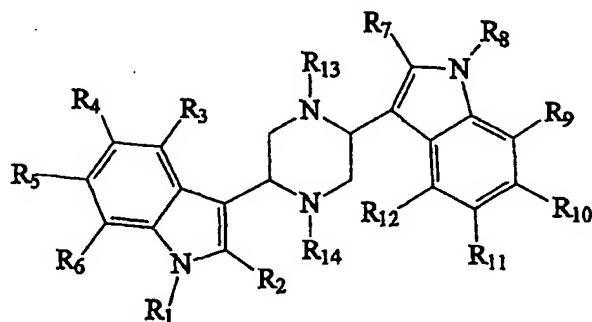
- 7 -

5 are disclosed.



**Formula 5**

In other embodiments, methods for making bisindole compounds of Formula  
5 6 are disclosed.



**Formula 6**

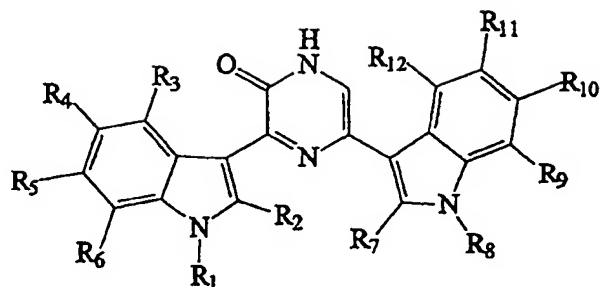
Compounds with Formula 6 are referred to herein as drarmacidins.

10 In some embodiments, methods for making bisindole compounds of Formula



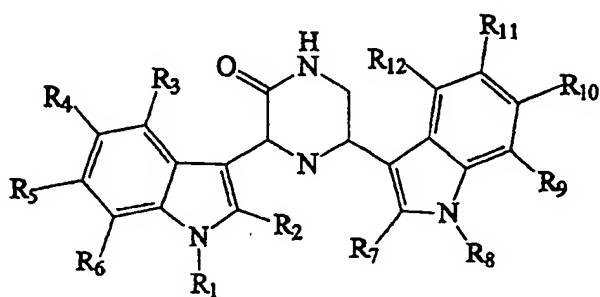
- 8 -

7 are disclosed.



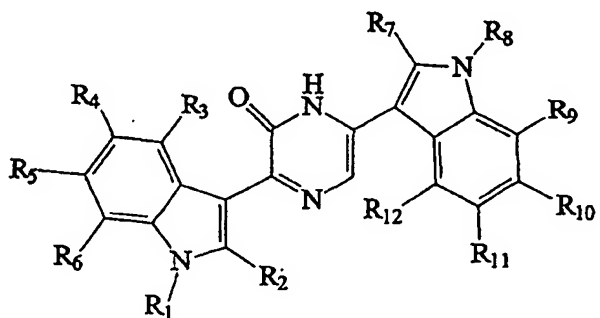
Formula 7

In other embodiments, methods for making bisindole compounds of Formula  
5 8 are disclosed.



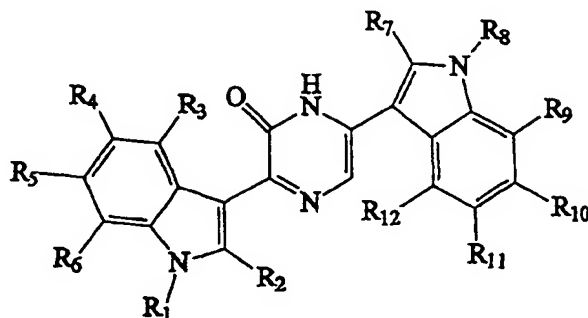
Formula 8

In other embodiments, methods for making bisindole compounds of Formula  
10 9 are disclosed.



Formula 9

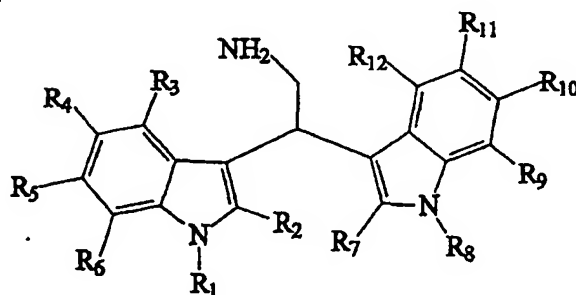
In other embodiments, methods for making bisindole compounds of Formula 10 are disclosed.



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**Formula 10**

In some embodiments, methods for making bisindole compounds of Formula 11 are disclosed.



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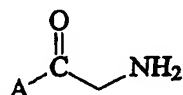
**Formula 11**

With reference to Formulas 1 through 11, the groups R<sub>1</sub> through R<sub>12</sub> are independently selected from the group consisting of hydrogen, hydroxy, halogen, lower aliphatic, particularly lower alkyl, lower alkoxy, and lower acyl. The term "lower" refers to organic radicals having 10 or fewer carbon atoms, including all straight and branched-chain isomers and stereoisomers. The term "aliphatic" refers to alkyl, alkenyl, and alkynyl radicals, including substituted derivatives thereof.

15

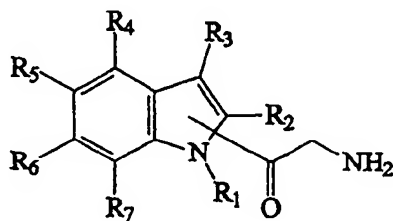
- 10 -

In another aspect, methods for making alpha amino ketones of Formula 12 are disclosed. Such alpha amino ketone synthons are particularly useful for synthesizing a wide variety of compounds, including compounds of Formulas 1 through 12. The methods for making these synthons disclosed herein provide synthetic advantages relative to other known methods.



Formula 12

With respect to Formula 12, A is a heterocycle comprising a ring system selected from the group of indole, pyridine, pyrimidine, purine, pyrrole, furan, thiophene, imidazole, benzimidazole, oxazole, thiazole, pyrazole, 3-pyrroline, pyrrolidine, quinolone, isoquinolone, carbazole, cyclic anhydride, cyclic imide, cyclic lactone, and the like. The alpha amino ketone portion may be joined to heterocycle A at any position on the heterocycle. In a particular embodiment, A is indole and the alpha amino ketone is attached at any position around the indole ring, such as shown in Formula 13.

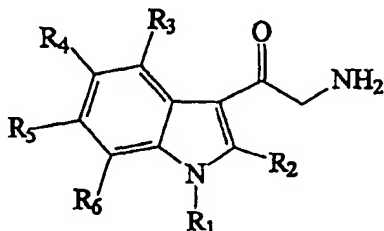


Formula 13

With reference to Formula 13, the alpha amino ketone group may replace any of the groups labeled R<sub>1</sub> through R<sub>7</sub>. The remaining R groups may be independently selected from the group consisting of hydrogen, hydroxy, halogen, lower aliphatic, particularly lower alkyl, lower alkoxy, and lower acyl.

- 11 -

In some embodiments, methods of making alpha amino ketones of Formula 11 are provided.



Formula 11

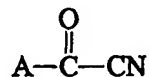
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With reference to Formula 11, the groups R<sub>1</sub> through R<sub>6</sub> are independently selected from the group consisting of hydrogen, hydroxy, halogen, lower aliphatic, particularly lower alkyl, lower alkoxy, and lower acyl.

10

#### DETAILED DESCRIPTION

The present invention includes a method for converting an acyl cyanide to an alpha amino ketone. In general, the method comprises providing an acyl cyanide, and converting the acyl cyanide to an alpha amino ketone, such as by catalytic hydrogenation. In some embodiments the acyl cyanide has the formula



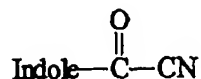
15

where A comprises a heterocycle selected from the group consisting of indole, pyridine, pyrimidine, purine, pyrrole, furan, thiophene, imidazole, benzimidazole, oxazole, thiazole, pyrazole, 3-pyrroline, pyrrolidine, quinolone, isoquinolone, carbazole, cyclic anhydride, cyclic imide, and cyclic lactone. The acyl cyanide group may be attached to heterocycle A in any position around the heterocycle.

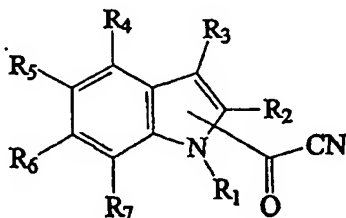
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- 12 -

In some embodiments, the acyl cyanide has the formula



where indole comprises an indole ring and, in particular embodiments, the acyl cyanide has the formula



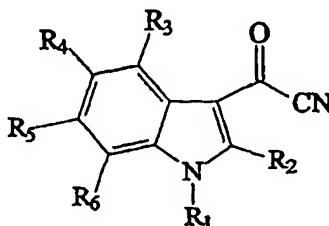
5

where the acyl cyano group may replace any of the groups labeled R<sub>1</sub> through R<sub>7</sub>.

The remaining R groups may be independently selected from the group consisting of hydrogen, hydroxy, halogen, lower aliphatic, particularly lower alkyl, lower alkoxy,

10 and lower acyl.

In more particular embodiments, the acyl cyanide has the formula



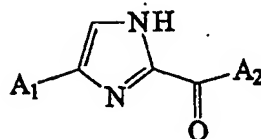
where R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub>, and R<sub>6</sub> are independently selected from the group consisting of hydrogen, hydroxy, halogen, lower aliphatic, lower alkoxy, and lower

15 acyl.

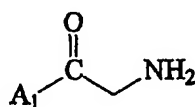
The acyl cyanide may be converted to the alpha amino ketone by exposing the acyl cyanide to hydrogen in the presence of a hydrogenation catalyst. In a particular embodiment, the hydrogenation catalyst is palladium carbon.

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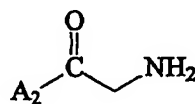
The present invention also includes a method for making an imidazole compound of formula



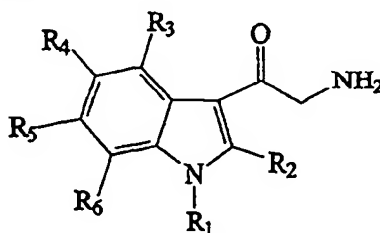
including topsentins. The disclosed embodiments comprised providing a first alpha amino ketone compound of formula



and providing a second alpha amino ketone compound of formula



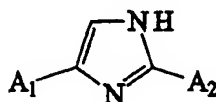
A mixture was formed comprising the first and second alpha amino ketone compounds, and the mixture was contacted with air to form the imidazole compound. A<sub>1</sub> and A<sub>2</sub> may be the same or different. In particular embodiments, A<sub>1</sub> and A<sub>2</sub> comprise an indole ring, and in more particular embodiments the first and second alpha amino ketone compounds have the formula



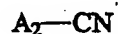
where R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub>, and R<sub>6</sub> are independently selected from the group consisting of hydrogen, hydroxy, halogen, lower aliphatic, lower alkoxy, and lower acyl.

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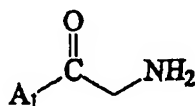
The present invention also provides a method for making an imidazole compound of formula



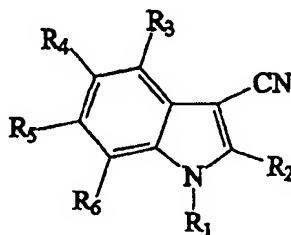
including nortopsentins Disclosed embodiments of the method comprise providing  
5 a cyano compound of formula



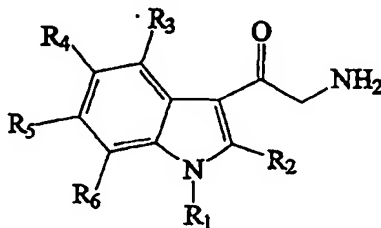
and providing an alpha amino ketone compound of formula



A mixture of the first and second compounds is formed, and heated to form the  
10 imidazole compound. Again A<sub>1</sub> and A<sub>2</sub> may be the same or different. In particular  
embodiments, A<sub>1</sub> and A<sub>2</sub> comprise an indole ring. In more particular embodiments,  
the cyano compound has the formula



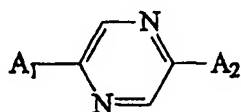
where R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub>, and R<sub>6</sub> are independently selected from the group  
15 consisting of hydrogen, hydroxy, halogen, lower aliphatic, lower alkoxy, and lower  
acyl, and the alpha amino ketone compound has the formula



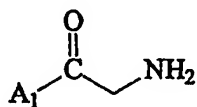
- 15 -

where  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_4$ ,  $R_5$ , and  $R_6$  are independently selected from the group consisting of hydrogen, hydroxy, halogen, lower aliphatic, lower alkoxy, and lower acyl.

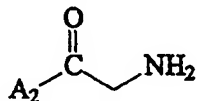
The present invention also provides a method for making a pyrazine  
5 compound of formula



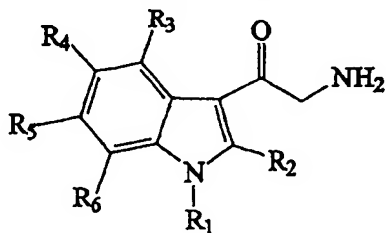
Disclosed embodiments comprised providing an alpha amino ketone compound of formula



10 and providing a second alpha amino ketone compound of formula



A mixture was formed comprising the first and second compounds. The mixture was heated while excluding air to form the pyrazine compound.  $A_1$  and  $A_2$  may be the same or different. In particular embodiments  $A_1$  and  $A_2$  comprise an indole ring,  
15 and in more particular embodiments, the two compounds have the formula

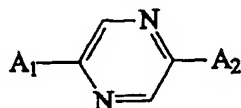


where  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_4$ ,  $R_5$ , and  $R_6$  are independently selected from the group consisting of hydrogen, hydroxy, halogen, lower aliphatic, lower alkoxy, and lower acyl.

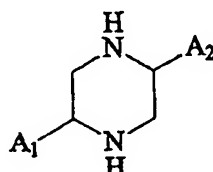


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Methods of reducing a pyrazine compound of formula

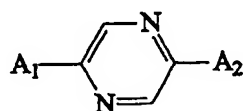


to form a piperazine compound of formula



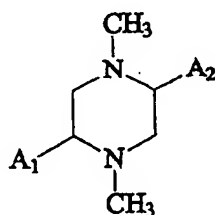
- 5 are also disclosed. In a particular disclosed embodiment, the pyrazine compound is reduced by exposing the pyrazine compound to  $\text{NaBH}_3\text{CN}$  in acetic acid solution. In a more particular disclosed embodiment, the piperazine compound formed by this method is Dragmacidin B.

According to the disclosure, pyrazine compounds of formula



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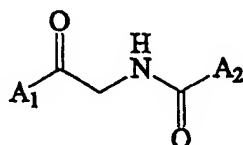
also may be reductively alkylated, such as methylated, to form piperazine compounds of formula



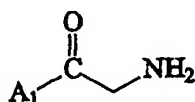
- 15 In a particular disclosed embodiment, reductive alkylation was performed by exposing the pyrazine compound to  $\text{NaBH}_3\text{CN}$  in formic acid solution. In a more particular disclosed embodiment, 2,5-bis(6'-bromo-3'-indolyl)piperazine was synthesized by this method.

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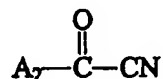
The present invention also provides methods for making amide compounds of formula



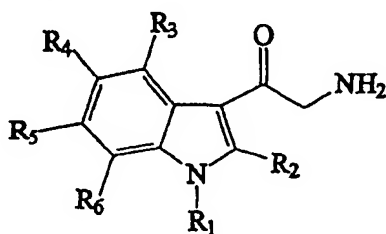
Disclosed embodiments of the method comprise providing an alpha amino ketone  
5 compound of formula



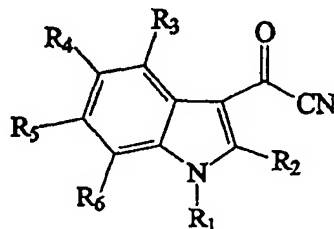
and providing an acyl cyanide compound of formula



A mixture of the first and second compounds is formed to make the amide  
10 compound. Again, A<sub>1</sub> and A<sub>2</sub> may be the same or different. In some embodiments, A<sub>1</sub> and A<sub>2</sub> comprise an indole ring. In more particular embodiments the alpha amino ketone compound has the formula



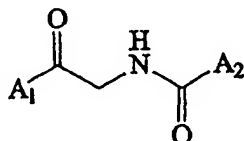
and the acyl cyanide compound has the formula



- 18 -

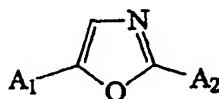
For both compounds,  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_4$ ,  $R_5$ , and  $R_6$  are independently selected from the group consisting of hydrogen, hydroxy, halogen, lower aliphatic, lower alkoxy, and lower acyl.

According to the disclosure, amide compounds of formula



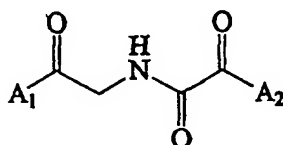
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may be cyclodehydrated to make an oxazole compounds of formula

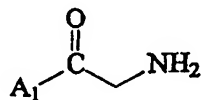


The present invention also provides methods for making amide compounds

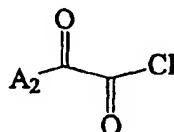
10 of formula



Disclosed embodiments of the method comprise forming a mixture of an alpha amino ketone compound of formula

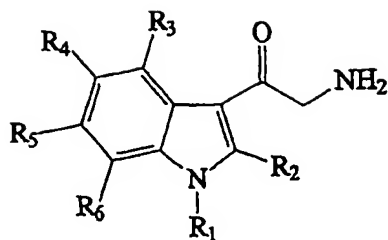


15 and a second compound of formula

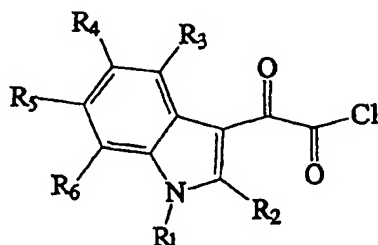


to make the amide compound.  $A_1$  and  $A_2$  may be the same or different. In one embodiment  $A_1$  and  $A_2$  comprise an indole ring. In more particular embodiments, the alpha amino ketone compound has the formula

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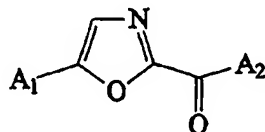


and the acyl cyanide compound has the formula

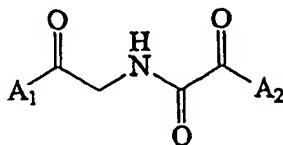


For both compounds, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub>, and R<sub>6</sub> are independently selected from the  
 5 group consisting of hydrogen, hydroxy, halogen, lower aliphatic, lower alkoxy, and lower acyl.

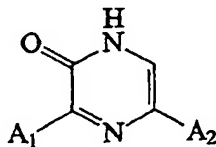
The present invention also provides a method for making a compound of formula



10 Disclosed embodiments of the method comprise heating an amide compound of formula

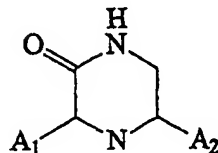


in ammonium hydroxide to form a first compound of formula

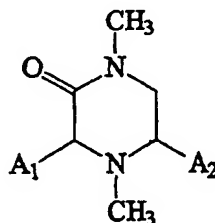


- 20 -

This compound can be reduced to form a compound of formula

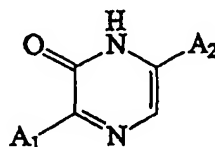


or reductively alkylated to form a compound of formula



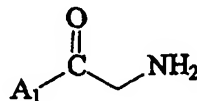
- 5 In particular embodiments, reduction was accomplished using  $\text{NaBH}_3\text{CN}$  in acetic acid solution and reductive methylation was accomplished using  $\text{NaBH}_3\text{CN}$  in formic acid solution.

The present invention further provides methods for making compounds of formulas

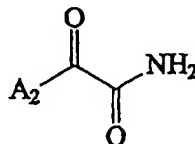


10

Disclosed embodiments of the method comprise making a mixture of a compound of formula



and a compound of formula



15

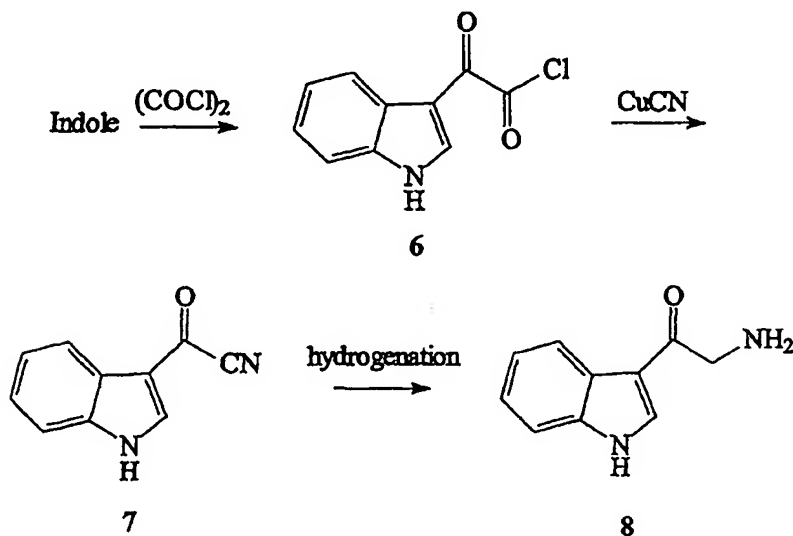
In one aspect, the methods disclosed herein provide short syntheses of bioactive topoisomerase II inhibitors, topoisomerase II inhibitors, and topoisomerase II inhibitors from readily available starting

- 21 -

materials. The methods also provide oxazole and pyrazine analogs of these bioactive compounds. The syntheses are highly symmetrical in nature, and represent an efficient entry to this bioactive class of bisindole compounds. Syntheses according to the disclosed methods may find further application to other latent  $\alpha$ -amino ketone derived natural products.

Persons of ordinary skill in the art will recognize that the following Schemes illustrate representative examples of general methods for making bisheterocyclic compounds and the intermediates used in those methods. Persons of ordinary skill in the art will further recognize that the indole rings in the following Schemes may have different substituents and substitution patterns from those illustrated. For example, the bromine atoms that appear in some of the compounds of these Schemes may appear at any position on the indole rings or may be replaced with other halogens.

In a disclosed embodiment, oxotryptamine 8 is prepared according to Scheme 1 below.

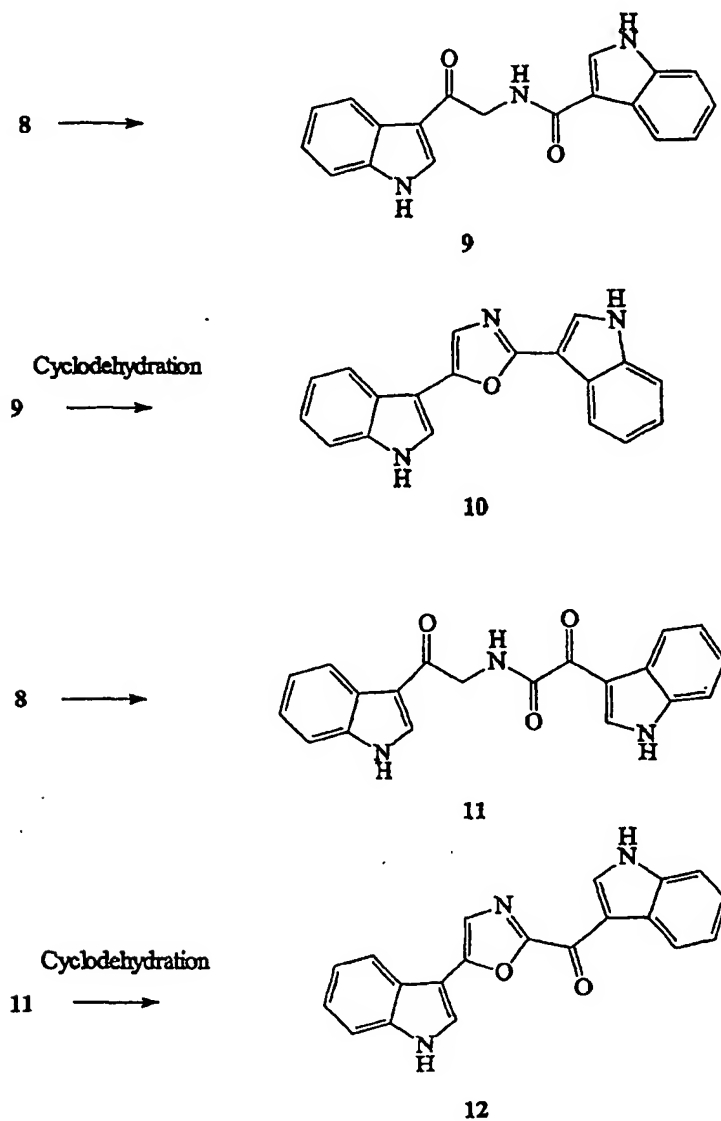


Scheme 1

Oxotryptamine synthons such as 8 may be utilized in a wide variety of methods as disclosed. In one disclosed embodiment the synthon is used to produce

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analogs of topsentins and nortopsentins with oxazole linkers. In a particular disclosed embodiment, unsubstituted oxazole analogs of topsentin and nortopsentin were synthesized according to Scheme 2 below.

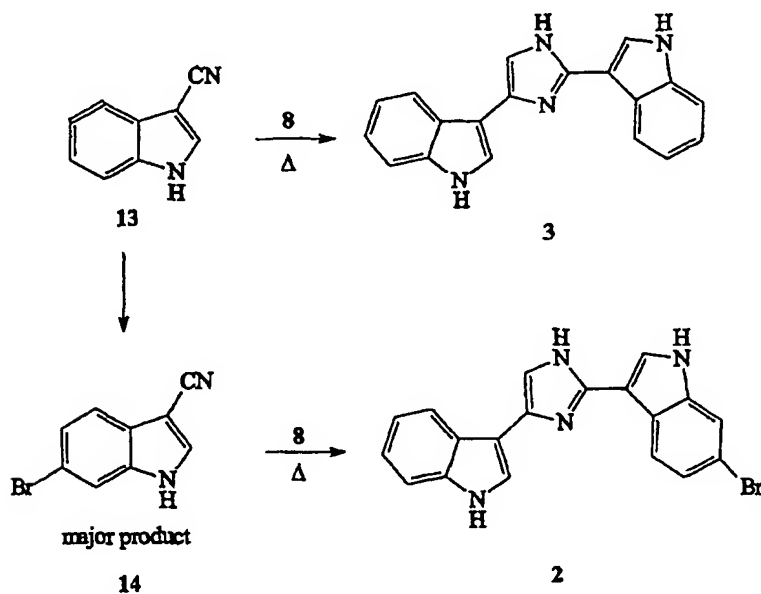
**Scheme 2**

For disclosed embodiments, the cyclodehydration steps in Scheme 2 were accomplished using  $\text{POCl}_3$ .

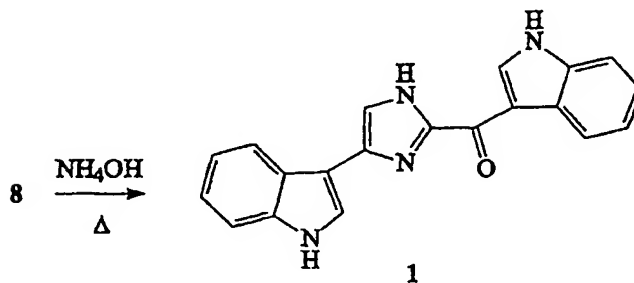
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In addition to oxazole analogs of topsentins and nortopsentins, methods for synthesizing topsentins and nortopsentins are disclosed. In particular disclosed embodiments, nortopsentins B 2 and D 3 were synthesized according to Scheme 3 below. In another disclosed embodiment, topsentin A was synthesized by head-to-

5 head condensation of oxotryptamine 8 according to Scheme 4 below.



Scheme 3

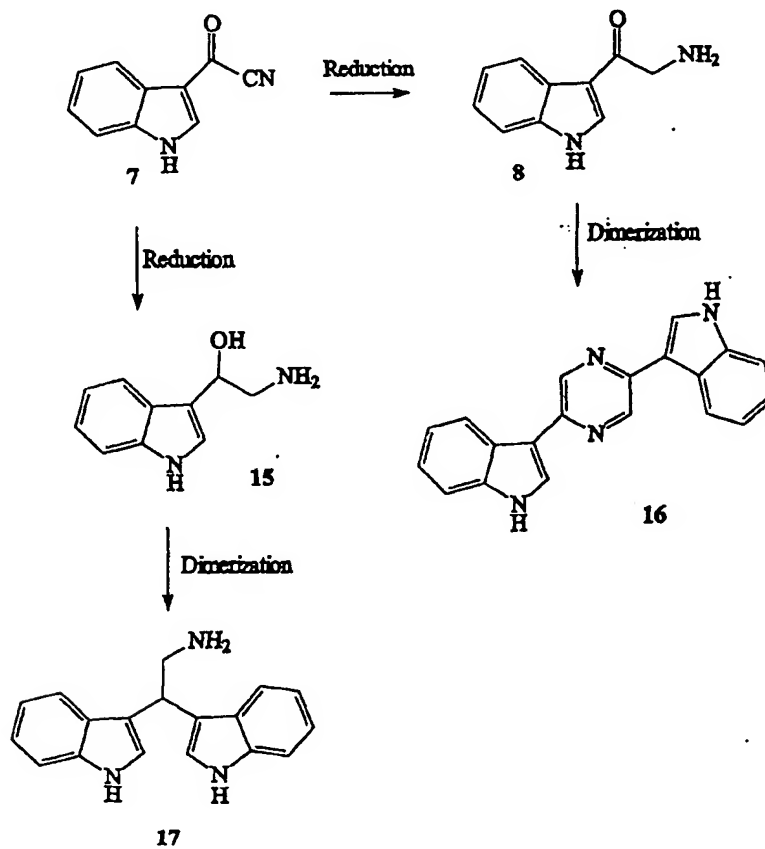


Scheme 4



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Pyrazine-linked bisindole compounds also may be synthesized using the disclosed oxotryptamine synthon approach. In one embodiment, an unsubstituted pyrazine-linked bisindole compound may be synthesized according to Scheme 5 below.

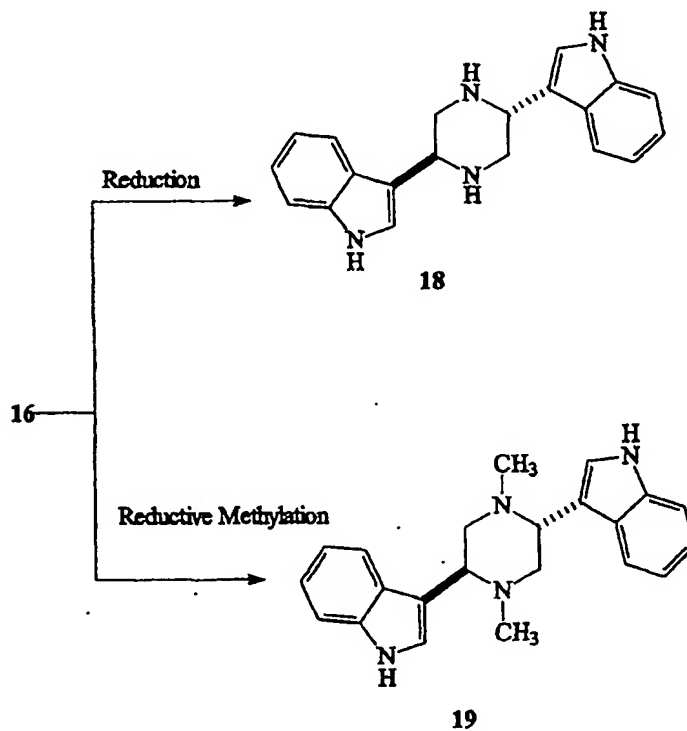


5

Scheme 5

- 25 -

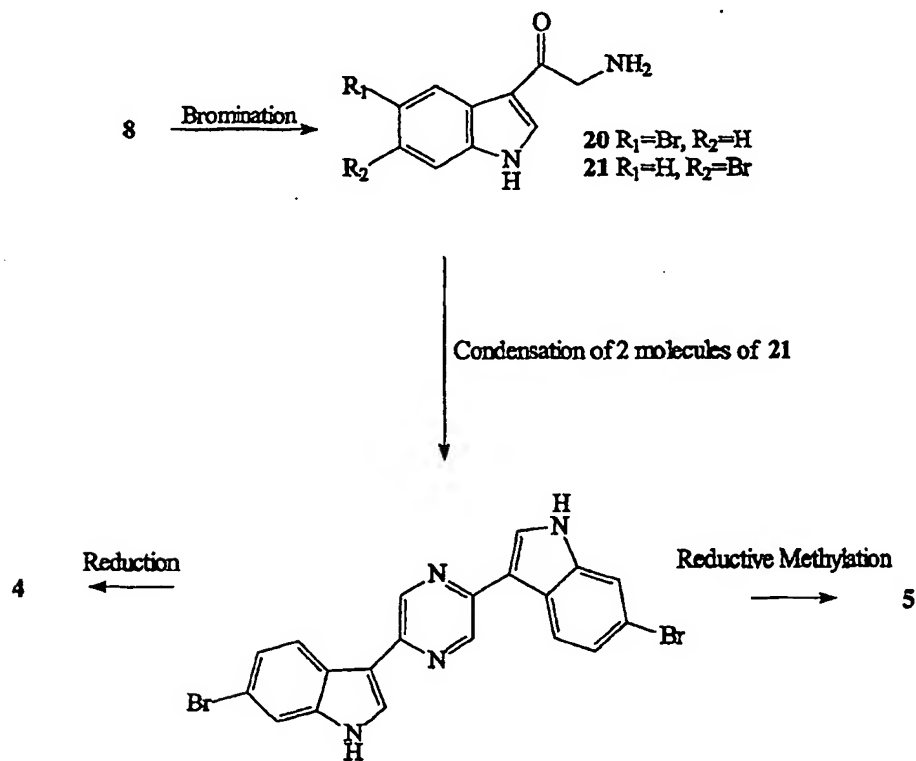
Piperazine-linked bisindole compounds also may be synthesized by selective reduction of pyrazine-linked bisindole compounds. For example, the synthesis of unsubstituted piperazine-linked and dimethyl piperazine-linked bisindole compounds may be accomplished according to Scheme 6 below.



Scheme 6

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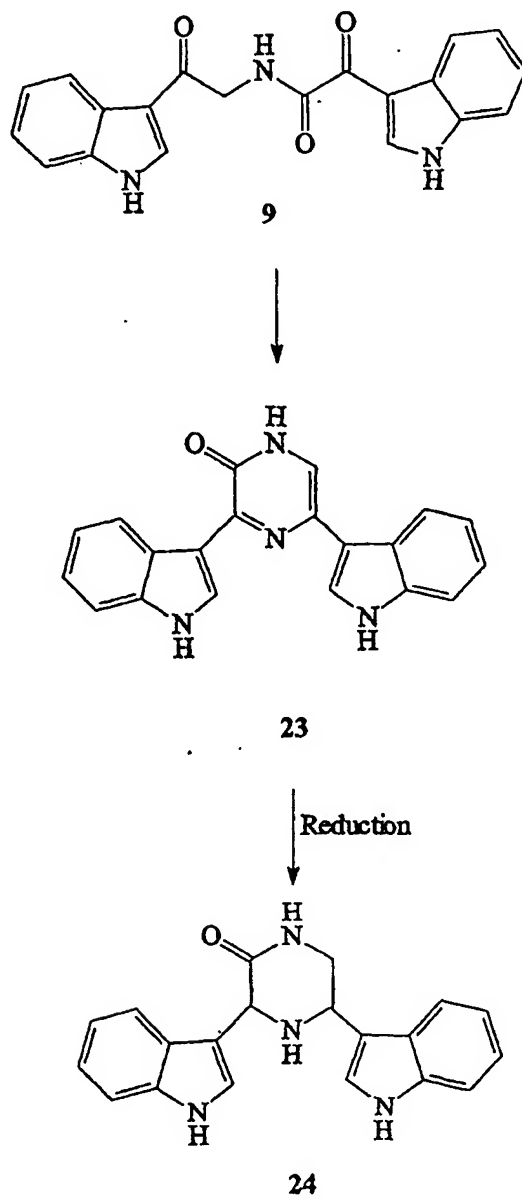
Drarmacidins and drarmacidin analogs may be synthesized from substituted oxotryptamine synthons through reduction or reductive alkylation of pyrazine-linked bisindole intermediates. For example, Scheme 7 outlines the synthesis of Dramacidin B 4 and 2,5-bis(6'-bromo-3'-indoyl)piperazine 5.



Scheme 7

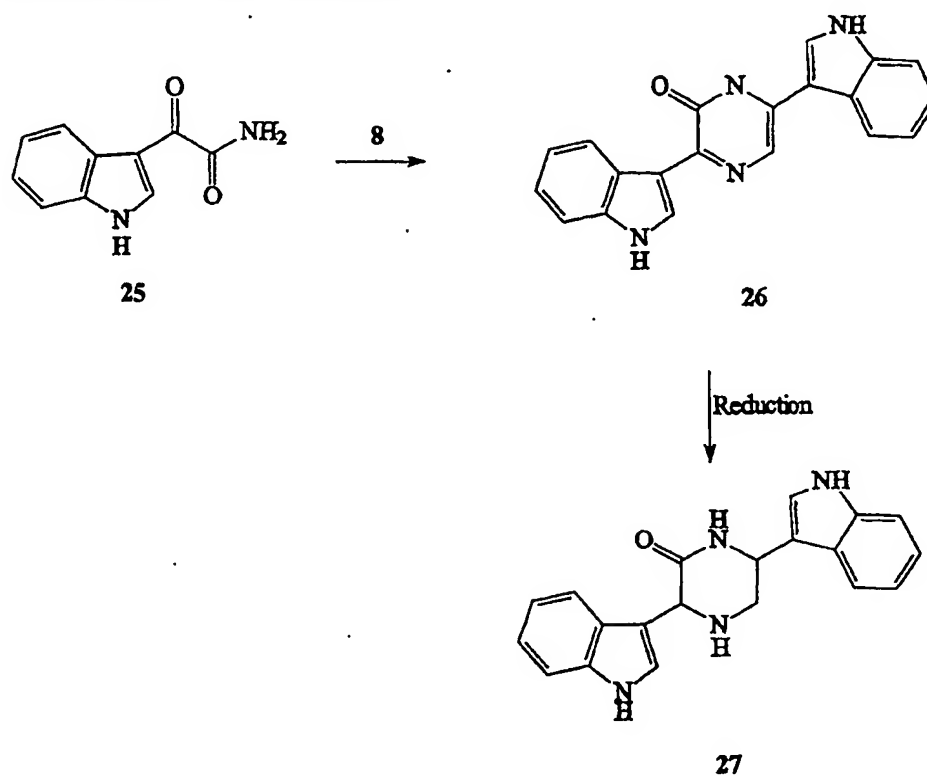
- 27 -

Scheme 8 illustrates the synthesis of a pyrimidinone-linked bisindole compound and its reduction.

**Scheme 8**

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Scheme 9 illustrates the synthesis of a different pyrimidinone-linked bisindole compound and its reduction.



Scheme 9

- 29 -

The following examples are provided solely to exemplify certain particular features of working embodiments. Working embodiments are also found in Miyake et al., *Org. Lett.*, 2000, 2, 2121 and Miyake et al., *Org. Lett.*, 2000, 2, 3185 which are incorporated by reference herein. The present invention should not be limited to the particular features described in the examples.

#### Example 1

10 This example describes the synthesis of acyl cyanide 7 from indole. The synthesis was carried out in two steps according to the method described in Hogan and Sainsbury, *Tetrahedron*, 1984, 40, 681, which is incorporated herein by reference. Briefly, indole is reacted first with oxalyl chloride to provide acid chloride 6. Acid chloride 6 was then reacted with copper (I) cyanide to provide acyl  
15 cyanide 7 as a colorless crystalline solid.

#### Example 2

This example describes the synthesis of oxotryptamine 8 from acyl cyanide 7. Four grams of acyl cyanide 7 was exposed to hydrogen in the presence of one  
20 gram of 10% Pd/C in acetic acid solution (23°C, 16h) to produce oxotryptamine 8 in 90% yield as the acetate salt.

Spectral data for free base: <sup>1</sup>H NMR (-300MHz d<sub>6</sub>-DMSO), δ 8.31 (s, 1H), 8.17 (bd, 1H, J=8), 7.46 (bd, 1H, J=8), 11.7 (bd, 1H), 7.22 ~ 7.15 (m, 2H), 3.89 (bs, 2H), 3.35 (br, 2H); <sup>13</sup>C NMR (300MHz, d<sub>6</sub>-DMSO), δ 195.3 (s), 136.5 (s), 133.0 (d),  
25 125.4 (s), 122.7 (d), 121.6 (d), 121.2 (d), 114.3 (s), 112.1 (d), 48.2 (t).

Spectral data for HCl salt: <sup>1</sup>H NMR (300 MHz d<sub>6</sub>-DMSO), δ 12.45 (bs, 1H, vanishing with D<sub>2</sub>O), 8.50 (d, 1H, J=2.9Hz), 8.36 (bs, 3H, vanishing with D<sub>2</sub>O), 8.15 (m, 1H), 7.52 (m, 1H), 7.23 ~ 7.15 (m, 2H), 4.34 (d, 2H, J=5.1, change to s with D<sub>2</sub>O)

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**Example 3**

This example describes the synthesis of amide 9. Acylation of oxotryptamine 8 with acyl cyanide 7 (neat) gave amide 9 in 95% yield.

5

**Example 4**

This example describes the synthesis of bis(3-indoyl)oxazole 10. Cyclodehydration of amide 9 with phosphorous oxychloride (23°C, 12 hours) produced bis(3-indoyl)oxazole 10 in 90% yield.

10

**Example 5**

This example describes the synthesis of amide 11. Acylation of oxotryptamine 8 with acid chloride 6 produced amide 11 in 92% yield.

Spectral data: <sup>1</sup>H NMR (300MHz, d<sub>6</sub>-DMSO), δ 12.25 (bs, 1H), 12.05 (bs, 1H), 8.90 (t, 1H, J=5.9), 8.82 (d, 1H, J=2.5), 8.51 (d, 1H, J=2.9), 8.26 (dd, 1H), 8.16 (dd, 1H), 7.54 (dd, 1H) 7.30 ~ 7.17 (m, 2H); <sup>13</sup>C NMR (300MHz, d<sub>6</sub>-DMSO), δ 189.2, 181.8, 163.7, 138.6, 136.4, 136.8, 133.8, 126.2, 125.4, 128.5, 122.9, 122.6, 121.9, 121.3, 121.1, 113.9, 112.6, 112.3, 112.2, 45.7.

15

**Example 6**

This example describes the synthesis of oxazole topsentin analog 12. Cyclodehydration of amide 11 with phosphorous oxychloride (23°C, 12 h) afforded the oxazole topsentin analog 12 in 85% yield.

20

**Example 7**

This example describes the synthesis of nortopsentin D 3. Condensation under neat conditions of commercially available 3-cyanoindole 13 (Aldrich, Milwaukee, WI) with oxotryptamine 8 produced nortopsentin D.

25

Spectral data: Free Base <sup>1</sup>H NMR (300MHz, d<sub>6</sub>-Acetone), δ 10.56 (s, 1H), 10.38 (s, 1H) 8.57 (dd, 1H, J=8.4), 8.05 (dd, 1H, J=8.4), 8.00 (d, 1H, J=2.0), 7.83 (s, 1H), 7.47 ~ 7.45 (m, 2H), 7.45 (s, 1H), 7.21 ~ 7.10 (m, 4H); Free Base <sup>1</sup>H NMR (300MHz, d<sub>6</sub>-DMSO), δ 12.30 (s, 1H), 11.37 (s, 1H), 11.18 (s, 1H), 8.41 (bd, 1H,

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J=7.1), 7.99 (bd, 1H, J=7.4), 7.93 (d, 1H, J=7.4), 7.74 (d, 1H, J=2.1), 7.41 (s, 1H), 7.45 ~ 7.43 (m, 2H), 7.19 ~ 7.07 (m, 4H); HCl salt <sup>1</sup>H NMR (300 MHz, d<sub>6</sub>-DMSO), δ 14.54 (bs, 1H), 14.15 (bs, 1H), 12.32 (bs, 1H), 11.73 (bs, 1H), 8.63 (d, 1H, J=2.9), 8.38 (d, 1H, J=2.6), 8.14 (bd, 1H, J=6.9), 7.95 (bd, 1H, J=6.9), 7.95 (s, 1H), 7.59 (bd, 1H, J=6.9), 7.51 (bd, 1H, J=7.8), 7.33 ~ 7.15 (m, 4H); HCl salt <sup>13</sup>C NMR (300MHz, d<sub>6</sub>-DMSO), δ 140.1 (s), 136.4 (s), 136.3 (s), 130.0, 127.9, 125.5, 124.01, 123.3, 123.0, 122.2, 121.1, 120.2, 119.5, 119.3, 112.6, 112.2 (d), 112.1 (d), 102.5, 99.0.

10

**Example 8**

This example describes the synthesis of 6-bromocyanindole 14. Direct bromination of 3-cyanindole 13 with NBS over silica in CH<sub>2</sub>Cl<sub>2</sub> (Mistry et al, *Tetrahedron Lett.*, 1986, 27, 1051, incorporated herein by reference) gave a 50% yield of bromindole 14 as the major product. Small amounts (10%) of the 5-substituted regioisomer were also observed. Although the yield was modest, the preparation of 14 requires only one step from commercially available 3-cyanindole and is easily separated from the minor regioisomer by flash chromatography. HMQC correlations confirmed the position of substitution.

20

**Example 9**

This example describes the synthesis of nortopsentin B 2. Condensation of oxotryptamine 8 with nitrile 14 under neat conditions produced nortopsentin B 2. All spectral data for synthetic nortopsentin B were identical to those reported for the natural material reported by Sakemi and Sun, *J. Org. Chem.*, 1991, 56, 4304.

25

**Example 10**

This example describes the preparation of topsentin A 1. Oxidative dimerization of oxotryptamine 8 in NH<sub>4</sub>OH and air at 100°C gave topsentin A 1 in 80% yield. All spectral data for synthetic topsentin A 1 were identical to those reported for the natural material reported by Bartik et al., *Can. J. Chem.*, 1987, 65, 2118.

30



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Spectral data: Free base  $^1\text{H}$  NMR (300MHz,  $d_6$ -Acetone),  $\delta$  12.12 (bs, 1H), 12.04 (bs, 1H) 11.14 (bs, 1H), 11.09 (bs, 1H), 10.38 (bs, 9.64 (d,  $J=3$ ), 9.41 (d,  $J=3.0$ ), 8.55 ~ 8.5 (m), 8.23 (bd), 8.09 (d), 7.97 (bd), 7.85 (d,  $J=2.4$ ), 7.72 (d,  $J=2.1$ ) 7.63 (d), 7.61 ~ 7.47 (m), 7.29 ~ 7.11 (m); Free base  $^1\text{H}$  NMR (300MHz,  $d_6$ -

5 DMSO),  $\delta$  13.21 (bs, \_\_), 13.12 (bs) 12.10 (bs), 12.04 (bs), 11.44 (bs), 11.22 (bs), 9.39 (d,  $J=3.0$ ), 9.18 (d,  $J=3.1$ ), 8.42 ~ 8.39 (m), 8.16 (d,  $J=7.4$ ), 8.10 (d,  $J=2.4$ ), 7.90 (d,  $J=7.4$ ), 7.83 (d,  $J=2.3$ ) 7.68 (d,  $J=2.1$ ), 7.62 (d,  $J=0.9$ ) 7.56 ~ 7.51 (m), 7.44 (bt,  $J=7.0$ ) 7.27 ~ 7.22 (m) 7.18 ~ 7.08 (m);  $^{13}\text{C}$  NMR (300MHz,  $d_6$ -Acetone),  $\delta$  177.14, 177.06, 146.6 (s), 140.2 (s), 138.0 (d), 137.9 (s), 137.8 (s), 137.6 (d), 137.4 (s),

10 137.35 (s), 131.0, 128.08 (d), 127.11 (d), 126.5 (s), 126.0 (s), 124.25, 123.87, 123.79, 123.21, 123.00, 122.79, 122.70, 122.41, 121.26, 121.03, 120.47, 120.33, 115.41, 115.03, 112.76, 112.34, 111.93, 106.58; HCl salt  $^1\text{H}$  NMR (300MHz,  $d_6$ -DMSO),  $\delta$  12.56 (bs, 1H), 11.67 (bs, 1H), 8.87 (bs, 1H), 8.32 ~ 8.29 (m, 1H), 8.13 (d, 1H,  $J=8.13$ ), 8.01 (s, 1H), 8.00 (d, 1H), 7.60 ~ 7.57 (m, 1H) 7.49 (d, 1H,  $J=7.5$ ),

15 7.33 ~ 7.27 (m, 2H), 7.23 ~ 7.13 (m, 4H);  $^{13}\text{C}$  NMR (300MHz,  $d_6$ -DMSO),  $\delta$  172.4 (s), 141.5 (s), 138.5 (d), 136.7 (s), 136.4 (s), 131.6 (s), 126.0 (s), 125.4 (d), 124.2 (s), 123.8 (d), 122.7 (d), 122.1 (d), 121.3 (d), 120.2 (d), 119.5 (d), 116.7 (d), 113.4 (s), 112.7 (d), 112.2 (d), 103.3 (s).

20

**Example 11**

This example describes the preparation of amino alcohol 15. Acyl cyanide 7 was reduced with lithium aluminum hydride ( $\text{LiAlH}_4$ ) according to the method disclosed by Burger and Hornbaker, *J. Am. Chem. Soc.*, 1952, 74, 5514 (incorporated herein by reference) to provide amino alcohol 15 in 60% yield.

25

Spectral data:  $^1\text{H}$  NMR (300MHz  $d_6$  DMSO),  $\delta$  11.01 (bs, 1H), 7.66 (d, 1H,  $J=7.8$ ), 7.39 (d, 1H,  $J=8.1$ ), 7.24 (s, 1H), 7.09 (t, d, 1H,  $J=7.5$ , 1.1), 6.99 (td, 1H,  $J=7.4$ , 1.0), 4.82 (dd, 1H,  $J=6.8$ , 5.2), 3.25 (b, 3H), 2.92 (dd, 1H,  $J=12.7$ , 5.2), 2.87 (dd,  $J=12.7$ , 6.8);  $^{13}\text{C}$  NMR (300MHz,  $d_6$ -DMSO),  $\delta$  137.3 (s), 126.8 (s), 123.03 (d), 121.78 (d), 120.18 (d), 119.16 (d), 118.42 (s), 112.32 (d), 69.73 (d), 49.64 (t).

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**Example 12**

This example describes the preparation of symmetrical dimer 17. Heating 15 in 4:1 xylene/EtOH solution at 130°C under a sealed atmosphere of argon followed by exposure to air and filtration gave dimer 17 (30%) and indole (20%) as the major products.

**Example 13**

This example describes the preparation of pyrazine 16. Heating oxotryptamine 8 in a 4:1 xylene/EtOH solution at 130°C for 3 days under a sealed atmosphere of argon followed by exposure to air and filtration gave pyrazine 16 in 85% yield.

Spectral data:  $C_{20}H_{14}N_4$ , Fab ( $C_{20}H_{15}N_4$ ) Mass 311.13001, Calculated. 311.12967;  $^1H$  NMR (300MHz) (in  $d_6$  DMSO),  $\delta$  11.62 (bs, 2H), 9.12 (s, 2H), 8.43 (d, 2H,  $J=7.2$ ), 8.22 (d, 2H,  $J=2.6$ ), 7.47 (d, 2H,  $J=7.6$ ), 7.21 ~ 7.11 (m, 4H);  $^{13}C$  NMR (300MHz)  $d_6$ -DMSO,  $\delta$  146.7 (size), 140.1 (d, 2C), 137.0 (s, 2C), 125.6 (d, 2C), 125.2 (s, 2C), 122.0 (d, 2C), 121.5 (d, 2C), 120.1 (d, 2C), 112.7 (s, 2C), 111.9 (d, 2C),

**Example 14**

This example describes the preparation of piperazine 18. Pyrazine 16 was reduced to piperazine 18 in 70% yield with  $NaBH_3CN$  in acetic acid using the reaction conditions described by Gribble et al., *J. Am. Chem. Soc.*, 1974, 96, 7812 (incorporated herein by reference). Only the thermodynamically more stable *trans* diequatorial isomer was detected.

Spectral data:  $^1H$  NMR (300MHz,  $d_6$ -DMSO),  $\delta$  10.85 (bs, 2H), 7.70 (d, 2H,  $J=7.73$ ), 7.34 (d, 2H,  $J=7.96$ ), 7.25 (d, 2H,  $J=2.1$ ), 7.05 (t, 2H,  $J=7.00$ ), 6.97 (t, 2H,  $J=6.94$ ), 4.07 (dd, 2H,  $J=10.1$ , 2.3), 3.18 (dd, 2H,  $J=11.5$ , 2.3), 2.87 (dd, 2H,  $J=11.5$ , 10.1), 2.58 (br, 2H);  $^{13}C$  NMR (300MHz,  $d_6$ -DMSO),  $\delta$  137.1 (s, 2C), 127.0 (s, 2C), 122.6 (2C), 121.7 (2C), 120.1 (2C), 119.0 (2C), 117.8 (2C), 112.3 (2C), 55.0 (2C), 54.2 (2C)

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**Example 15**

This example describes the preparation of dimethyl piperazine 19. Pyrazine 16 was treated with  $\text{NaBH}_3\text{CN}$  in formic acid under conditions similar to those used in Example 14. Pyrazine 16 underwent reductive methylation to provide dimethyl  
5 piperazine 19 in 60% yield.

**Example 16**

This example describes the synthesis of halogenated oxotryptamines 20 and 21. Oxotryptamine 8 was brominated with NBS over silica in  $\text{CH}_2\text{Cl}_2$  (Mistry et al,  
10 *Tetrahedron Lett.*, 1986, 27, 1051, incorporated herein by reference) to give an isomeric mixture of 5- and 6-substituted indole derivatives 20 and 21 in an approximate 2:1 ratio, respectively. The isomers were separated by flash chromatography.

**Example 17**

15 This example describes the synthesis of pyrazine 22. Condensation of halogenated oxotryptamine 22 by heating ( $130^\circ\text{C}$ ) in 4:1 xylene/EtOH under a sealed atmosphere of argon for 3 days followed by exposure to air and filtration gave pyrazine 22 in 75% yield.

20

**Example 18**

This example describes the synthesis of dragmacidin B 4. Selective reduction of the pyrazine ring using  $\text{NaBH}_3\text{CN}$  in formic acid (See, Example 14 for conditions) gave dragmacidin B 4 in 70% yield. Spectral data were consistent with  
25 those reported for natural dragmacidin B.

**Example 19**

This example describes the synthesis of 2,5-bis(6'-bromo-3'-indoyl) piperazine 5. Reductive methylation using  $\text{NaBH}_3\text{CN}$  in acetic acid (See, Example  
30 14 for conditions) gave piperazine 5 in 60% yield.

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**Example 20**

This example describes the synthesis of compound 23. Compound 9 (0.05g) was heated in  $\text{NH}_4\text{OH}$  at  $100^\circ\text{C}$  for 30 hours under nitrogen to provide 23 in 70% yield.

5        Spectral data:  $^1\text{H}$  NMR (300MHz,  $\text{d}_6$ -DMSO),  $\delta$  12.24 (bs, 1H), 11.60 (bs, 1H), 11.32 (bs, 1H), 8.87 (d, 1H,  $J=2.8$ ), 8.77 (d, 1H,  $J=7.6$ ), 8.02 (d, 1H,  $J=7.7$ ), 7.83 (d, 1H,  $J=2.5$ ), 7.48 (s, 1H), 7.50 ~ 7.46 (m, 2H), 7.23 ~ 7.06 (m, 4H);  $^{13}\text{C}$  NMR (400MHz,  $\text{d}_6$ -DMSO),  $\delta$  154.6 (s), 151.2 (s), 137.7 (s), 137.1 (s), 132.2 (d), 130.9 (s), 126.9 (s), 125.4 (s), 124.1 (d), 123.5 (d), 123.0 (d), 122.3 (d), 121.3 (d),  
10    120.8 (d), 120.2 (d), 117.2 (s), 114.2 (s), 112.9 (d), 112.8 (d), 112.6 (d).

**Example 21**

This example describes the synthesis of compound 24. Compound 23 (0.016g) was treated with 0.125g  $\text{NaBH}_3\text{CN}$  in 15 mL of acetic acid to provide 24.

15

**Example 22**

This example describes the synthesis of compound 26. Compound 25 (0.3g) was reacted neat with compound 8 (0.2g) at  $220^\circ\text{C}$  for 4 hours to provide 26 in 60% yield.

20        Spectral data:  $^1\text{H}$  NMR (300 MHz,  $\text{d}_6$ -DMSO)  $\delta$  12.21 (br, 1H), 11.73 (br, 1H), 11.50 (br, 1H), 8.74 (bs, 1H), 8.68 (d, 1H,  $J=7.8$ ), 8.10 (d, 1H,  $J=2.2$ ), 7.25 (br, 2H), 7.50 ~ 7.45 (m, 2H), 2.25-7.11 (4H);  $^{13}\text{C}$  NMR (400 MHz,  $\text{d}_6$ -DMSO)  $\delta$  156.4, 146.7, 137.7, 137.1, 130.9, 127.1, 126.8, 124.9, 123.6, 123.1, 122.9, 121.4, 121.0, 120.7 (d), 113.1, 112.8, 112.5, 107.7.

25

**Example 23**

This example describes the synthesis of compound 27. Compound 26 is treated with  $\text{NaBH}_3\text{CN}$  in acetic acid to provide 27.

30        The present invention has been described with respect to certain embodiments. The scope of the invention should not be limited to these described embodiments, but rather should be determined by reference to the following claims.

- 36 -

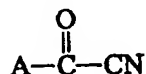
We Claim:

1. A method for converting an acyl cyanide to an alpha amino ketone, comprising:

providing an acyl cyanide; and

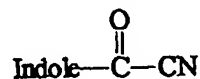
5 hydrogenating the acyl cyanide to convert the acyl cyanide to an alpha amino ketone.

2. The method of claim 1 wherein the acyl cyanide has the formula



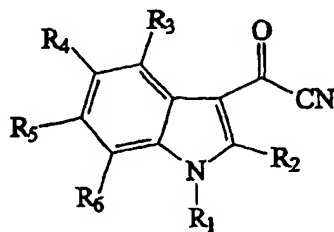
10 where A comprises a heterocycle selected from the group consisting of indole, pyridine, pyrimidine, purine, pyrrole, furan, thiophene, imidazole, benzimidazole, oxazole, thiazole, pyrazole, 3-pyrroline, pyrrolidine, quinolone, isoquinolone, carbazole, cyclic anhydride, cyclic imide, and cyclic lactone.

15 3. The method of claim 2, wherein the acyl cyanide has the formula



where indole comprises an indole ring.

4. The method of claim 3, wherein the acyl cyanide has the formula



20

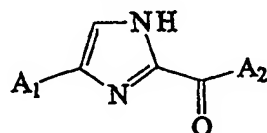
where  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_4$ ,  $R_5$ , and  $R_6$  are independently selected from the group consisting of hydrogen, hydroxy, halogen, lower aliphatic, lower alkoxy, and lower acyl.

- 37 -

5. The method of claim 1, wherein hydrogenating the acyl cyanide to convert the acyl cyanide to an alpha amino ketone comprises exposing the acyl cyanide to hydrogen in the presence of a hydrogenation catalyst.

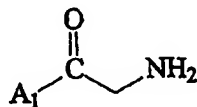
5 6. The method of claim 5, wherein the hydrogenation catalyst is palladium carbon.

7. A method for making an imidazole compound of formula

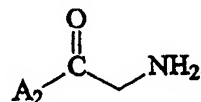


10 comprising:

providing a first compound of formula



providing a second compound of formula



15 forming a mixture of the first and second compounds; and  
contacting the mixture with air to form the imidazole compound.

8. The method of claim 7, wherein  $A_1$  and  $A_2$  are the same.

20 9. The method of claim 8, wherein  $A_1$  and  $A_2$  comprise an indole ring.

10. The method of claim 7, wherein the imidazole compound is a bisindole compound.

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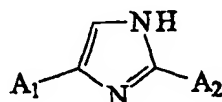
11. The method of claim 10, wherein the bisindole compound is a topsentin.

12. The method of claim 11, wherein the topsentin is topsentin A.

5

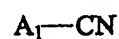
13. The method of claim 7, wherein  $A_1$  and  $A_2$  are different.

14. A method for making an imidazole compound of formula

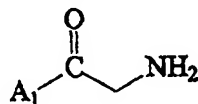


10 comprising:

providing a first compound of formula



providing a second compound of formula



15 forming a mixture of the first and second compounds; and heating the mixture to form the imidazole compound.

15. The method of claim 14, wherein  $A_1$  and  $A_2$  are the same.

20 16. The method of claim 15, wherein,  $A_1$  and  $A_2$  comprise an indole ring.

17. The method of claim 14, wherein the imidazole compound is a bisindole compound.

25 18. The method of claim 17, wherein the bisindole compound is a nortopsentin.

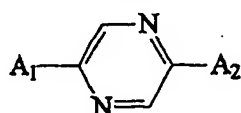
- 39 -

19. The method of claim 18, wherein the nortopsentin is nortopsentin B.

20. The method of claim 18 wherein the nortopsentin is nortopsentin D.

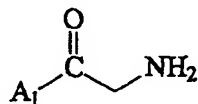
5 21. The method of claim 14, wherein A<sub>1</sub> and A<sub>2</sub> are different.

22. A method for making a pyrazine compound of formula

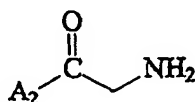


comprising:

10 providing a first compound of formula



providing a second compound of formula



forming a mixture of the first and second compounds; and

15 heating the mixture while excluding air to form the pyrazine compound.

23. The method of claim 22, wherein A<sub>1</sub> and A<sub>2</sub> are the same.

24. The method of claim 23, wherein, A<sub>1</sub> and A<sub>2</sub> comprise an indole ring.

20

25. The method of claim 22, wherein the pyrazine compound is a bisindole compound.

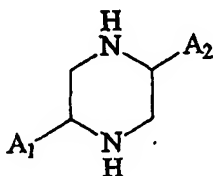
26. The method of claim 22, wherein A<sub>1</sub> and A<sub>2</sub> are different.

25



- 40 -

27. The method of claim 22, further comprising a step of reducing the pyrazine compound to form a piperazine compound of formula



28. The method of claim 27, wherein the step of reducing the pyrazine compound comprises exposing the pyrazine compound to  $\text{NaBH}_3\text{CN}$  in acetic acid solution.

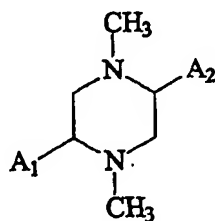
29. The method of claim 27, wherein the piperazine compound is a bisindole compound.

10

30. The method of claim 29, wherein the bisindole compound is dragnacidin B.

31. The method of claim 22, further comprising a step of reductively methylating the pyrazine compound to form a piperazine compound of formula

15



32. The method of claim 31, wherein the step of reductively methylating the pyrazine compound comprises exposing the pyrazine compound to  $\text{NaBH}_3\text{CN}$  in formic acid solution.

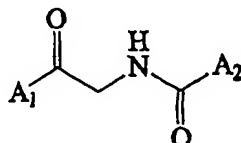
20

33. The method of claim 31, wherein the piperazine compound is a bisindole compound.

- 41 -

34. The method of claim 31, wherein the bisindole compound is 2,5-bis(6'-bromo-3'-indolyl)piperazine.

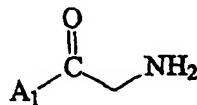
35. A method for making an amide compound of formula



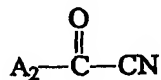
5

comprising:

providing a first compound of formula



providing a second compound of formula



10

forming a mixture of the first and second compounds to form the amide compound.

36. The method of claim 35, wherein A1 and A2 are the same.

15

37. The method of claim 35, wherein, A1 and A2 comprise an indole ring.

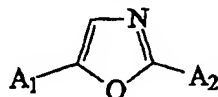
38. The method of claim 35, wherein the amide compound is a bisindole compound.

20

39. The method of claim 35, wherein A1 and A2 are different.

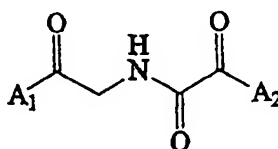
- 42 -

40. The method of claim 35, further comprising a step of cyclodehydrating the amide compound to form an oxazole compound of formula



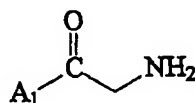
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41. A method for making an amide compound of formula



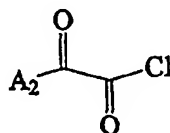
comprising:

providing a first compound of formula



10

providing a second compound of formula



forming a mixture of the first and second compounds to form the amide compound.

15

42. The method of claim 41, wherein A<sub>1</sub> and A<sub>2</sub> are the same.

43. The method of claim 41, wherein, A<sub>1</sub> and A<sub>2</sub> comprise an indole ring.

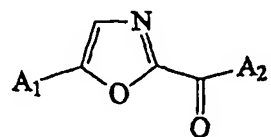
44. The method of claim 41, wherein the amide compound is a bisindole compound.

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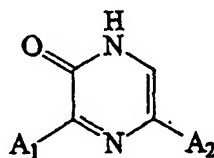
45. The method of claim 41, wherein  $A_1$  and  $A_2$  are different.

46. The method of claim 41, further comprising a step of cyclodehydrating the amide compound to form an oxazole compound of formula



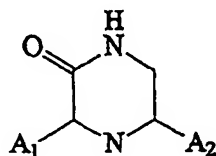
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47. The method of claim 41, further comprising a step of heating the amide compound in ammonium hydroxide to form a first compound of formula



10

48. The method of claim 47, further comprising a step of reducing the first compound to form a second compound of formula

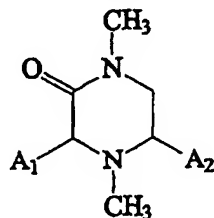


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49. The method of claim 48, wherein the step of reducing the compound comprises exposing the first compound to  $\text{NaBH}_3\text{CN}$  in acetic acid solution.

- 44 -

50. The method of claim 47, further comprising a step of reductively methylating the first compound to form a second compound of formula



5 51. The method of claim 50, wherein the step of reductively methylating the first compound comprises exposing the first compound to  $\text{NaBH}_3\text{CN}$  in formic acid solution.

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US01/18584

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C07D 209/12

US CL : 548/491

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 548/491

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,936,098 A (YASUDA et al) 10 August 1999, col. 1, lines 26-46.	4

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents	T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E" earlier document published on or after the international filing date	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"I" document which may throw doubt on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"G" document member of the same patent family
"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

08 AUGUST 2001

Date of mailing of the international search report

11 OCT 2001

Name and mailing address of the ISA/US  
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# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US01/18584

## BOX I. OBSERVATIONS WHERE CLAIMS WERE FOUND UNSEARCHABLE

2. Where no meaningful search could be carried out, specifically:

In these claims, the virtual unlimited scope of the subject matter (e.g. reactants and reactions conditions) and where present, the numerous variables and their voluminous, complex meanings makes it virtually impossible to determine the full scope and complete meaning of the claimed subject matter. As presented the claimed subject matter cannot be regarded as being a clear and concise description from which protection is sought and as such the listed claims do not comply with the requirements of PCT Article 6. Thus it is impossible to carry out a meaningful search on same.

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US01/18584

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
  
2. ☒ Claims Nos.: 1-5 and 5-51  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:  
  
Please See Extra Sheet.
  
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 64(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
  
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.  
☐ No protest accompanied the payment of additional search fees.